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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,974	06/20/2001	Mark Laurence Brader	X-11869	9992

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,974	BRADER ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,36,37,40,41,43,44 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 36-37, 40-41, 43-44 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 20, 2005 has been entered.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Claim Disposition

3. Claims 1-33, 35, 38-39, 42 and 45-46 have been cancelled. Claims 34, 36-37, 40-41, 43-44 and 47 are pending and are under examination.

Rejection - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34, 36-37, 40-41, 43-44 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a shelf stable solution formulation comprising GLP-1, a preservative and tonicity modifier and a pH of about 8.2-8.8. The specification on page 6 disclose that the present inventions provides a shelf stable formulation of GLP-1, GLP-1 analogs and GLP-1 derivatives; and the amide forms thereof. A skilled artisan cannot envision the detailed chemical structure of all the derivatives encompassed in the claims. The claims are directed to a large variable genus of GLP-1 associated molecules. The specification fails to provide any additional representative species of the claimed genus, to show that applicant was in possession of the claimed genus.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a

known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. Claims 34, 36-37, 40-41, 43-44 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a shelf stable solution formulation comprising SEQ ID NO: 2 and GLP-1 analogs known in the art, does not reasonably provide enablement for any GLP-1 derivative or variant or amide form thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

Undue experimentation would required to construct all the possible derivatives/variants encompassed in the claimed invention and test the same for a shelf-stable solution formulation to be administered to a patient suffering from diabetes. The art recognizes GLP-1 analogs, however, the changes contemplated in the claimed invention surpasses such a disclosure. Claim 34 for example provides a laundry list of changes that can be made, however, none is exemplified. SEQ ID NO:2 can have

specific substitutions at a R1, X, Y, Z or R2 position (see for example claim 41), however, claim 34 recites "at least one modification" in association with a laundry list of possibilities, devoid of a showing of said derivative and its applicability. The art recognizes that GLP-1 analogs play a role in the treatment of diabetes, however, there is no showing of all the derivatives encompassed in the claims (see for example claim 40). No direct correlation is made between structure and function. In addition, there are no indicia as to what residue substitution can be tolerated to retain stability and if the position of the residue will affect the formulation adversely. The specification on pages 9-10 provides a discussion of GLP-1 analogs and derivatives, however, the substitutions contemplated is limited to specific residues at specific positions in the sequence. Therefore, a skilled artisan would have to engage in undue experimentation to able to determine if all possible substitutions result in a shelf stable formulation and if there are positions within the molecule that cannot tolerate the modifications contemplated, to practice the claimed invention commensurate in scope with the claims.

It is in no way predictable what changes can be tolerated in a protein's structure. Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification,

for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The specification lacks guidance with regard to whether, for example, a substitution of an alanine at position 3 would be detrimental to the formulation, and in

term the claimed method of treatment. In view of the foregoing, the specification lacks adequate guidance/direction to be enabling.

The working examples provided do not demonstrate or describe the claimed invention to enable the full scope of the claims.

The nature of the invention relates to a stable formulation in solution comprising GLP-1 with substitutions of specific residues at a specified position. The claimed product can also have a substitution of at least one additional amino acid in the protein structure. The prior art teaches GLP-1 analogs, with substitutions that retain stability, however, no support was found for all the substitutions claimed having no adverse effect on the formulation. For example, GLP-1 analogs (a molecule having one or more amino acid substitution) are disclosed in WO 91/11457 and they include modification such as a substitution of glycine at position 26 or 34, and lists a number of substitutions that can also occur at positions 36, 31, 21, 22, 15 etc. Specific positions having specific residue substitutions are provided. The claimed formulation reads on at least one of the prescribed residue and any others from the laundry list of amino acids and any amounts since "at least one" includes, 10, 20, etc. There is no indication in the instant specification as to whether position 26 will have a "valine-isoleucine-leucine or valine-valine-valine, for example. These tripeptides are encompassed in the "at least one" recitation as well as more than three residues with a variety of arrangements.

The prior art generally acknowledges that a structural change in a protein's sequence can affect the function of the protein. Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) teach that substitution of an amino

acid as alanine, as a result of the changes to the nucleotide sequence, have a significant functional impact on the polypeptide. Therefore, the substitutions contemplated within SEQ ID NO:2 can result in an unstable product, rendering the invention as unpredictable.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of derivatives of GLP-1. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making

and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 34, 36-37 and 40 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claim 34 and the dependent claims hereto are indefinite because the claim recites positions such as "position 26, 34, 36, 31, 18, 16, 22, 23, 8 etc." without a structure *per se* that corresponds to the positions. It is noted that the claim recites GLP-1 (7-34), GLP-1(7-35) which are known GLP analogs in the art, however, it is unclear from the claim language if positions 26, 34, 36, 31, 18, 16, 22, 23, 8 etc., are the same in all of the GLP-1 analogs.

Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 34, 36, 40-41, 43 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoffman (U.S. Patent No. 6,358,924, June 1, 2000), based on the broad recitation of a pH of "about 8.2 to about 8.8" which is undefined in the instant specification.

Hoffman teaches a stable solution formulation comprising GLP-1 peptides, derivatives and GLP-1 analogs, for example GLP-1 (7-34) or the amide forms thereof, a pharmaceutically acceptable preservative (m-cresol) and a tonicity-modifying agent (glycerin) (claim 34, see columns 2, 4 and 5 of the patent). Hoffmann also teach a pH range of 6.5-9.0 which falls within the recited range. Further, the Hoffmann patent exemplifies a pH of 8.0 which is "about 8.2" as recited in the claims, as there is no limiting definition for "about" in the specification, thus has been interpreted as $\pm$ 5 (claim 34). The formulation taught by Hoffmann contains at least one substitution selected from the group consisting of a glycine, serine, cysteine etc., at position 26 (see column 5), said 'at least one substitution' is identical to the instant application structure (i.e. SEQ ID NO:2 and the formulation in the instant claims 34 and 43). Hoffmann discloses that in the formulation arginine is replaced with lysine at position 34 (claim 36, see column 5, item a). Additionally, Hoffmann has a method of treating a person having diabetes or other conditions in which the administration of a GLP-1-like molecule is indicated

(column 2, claims 40 and 47 of the instant specification). Further, the formulation recited in the instant claim 41 is anticipated as Hoffmann discloses the same formulation (see the bottom of column 4 of the patent). Therefore, the limitations of the claims are met by the reference.

Applicant's Arguments

8. The Amendment filed on September 20, 2005 has been considered, however, is not fully persuasive. On page 5 of the response it is stated that the cited Hoffman reference cannot be used under 35 U.S.C. 103 (a) in combination with a 102(e) as the patent and instant application have the same assignee. Note that the rejection has been amendment to withdrawn the 103 portion. In addition, Applicant respectfully requested the withdrawal of the 102 (e) on the grounds that Hoffmann does not disclose all the elements of the claims. Applicant state that the pH range exemplified by Hoffman is pH 8.1, whereas the claimed invention is directed to a pH range of 8.2-8.8. This argument is not convincing as the claimed invention is directed to a pH of 'about 8.2 to about 8.8'. The instant specification does not provide a definition for "said about language, thus the disclosure of Hoffmann anticipates the claimed invention because "about 8.2" is a pH of "8.1". The art generally recognizes the term about to mean $\pm$5. Additionally, Hoffmann discloses a pH range of 6.0 to 9.0, which anticipates the claimed invention. It is further stated that one factor that plays a role in the stability of GLP-1 formulations is the maintenance of pH at a prescribed level. Applicant is arguing a limitation that is not present in the claims as the claims do not *per se* recite a prescribed range as "about" is

not a discrete measurement. Applicant's discussion regarding a broad and narrow range is noted, however, not persuasive as the limitations of the claims are met by the cited Hoffmann reference for the reasons of record and presented herein.

It is noted that the response did not address the issues raised under 35 U.S.C. 112, first paragraph. Note that the rejections remains, however, has been amended. Note also that a new rejection has been instituted under 35 U.S.C. 112, first paragraph written description for the reasons stated above. This response is deemed fully responsive to the issues raised by applicant.

Conclusion

9. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS 2/8/06

Patent Examiner

HOPE ROBINSON
PATENT EXAMINER